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G. E. DE SCHWEINITZ, M.D.
PHILADELPHIA.

Reprinted from The Journal of the American Medical Association, February 9, 1907, Vol. xlviii, pp. 502-506.

CHICAGO:
PRESS OF AMERICAN MEDICAL ASSOCIATION
ONE HUNDRED AND THREE DEARBORN AVENUE.
1907.

AUTOINTOXICATION IN RELATION TO THE EYE.*

G. E. DE SCHWEINITZ, M.D.
PHILADELPHIA.

INTRODUCTION.

Observers differ, often widely, in their conception of autointoxication; hence it is necessary first to describe, briefly at least, what is included in the term in so far as the present contribution is concerned.

As W. Louis Chapman[1] points out, "the variety of definitions given for this state bears testimony to the difficulty of obtaining one which is terse yet comprehensive." The one advocated by Albu[2] is as follows: "Autointoxication is a poisoning of the organism by the products of its own metabolism, which may be normal, but accumulated in excessive quantities, or they may be abnormal. Among the latter it is necessary to distinguish between those which are subject to further transposition, and those which are formed not at all or only in slight degree in the healthy organism."

Food in its passage from the mouth to the large intestine is subject to complex chemical processes which include oxidation, reduction, decomposition and synthesis. The results are the end products of assimilation, water, inorganic salts, urea, uric acid, etc. Between the introduction into the mouth of nourishment and the appearance of these ultimate substances occurs the development of the intermediary products of metabolism, called by Gautier the leucomaines. Normally, they are oxidized, reduced, decomposed, or united with other

* Read in the Section on Ophthalmology of the American Medical Association, at the Fifty-seventh Annual Session, June, 1906.

1. Chapman: "Autointoxication as a Cause and Complication of Disease," Fiske Fund Prize Essay, p. 9.

2. Albu: "Ueber die Autointoxicationen des Intestinal Tractus," Berlin, 1895, p. 3.

substances in the body. Abnormally, if the outlet of metabolism meets with a check, they accumulate and are reabsorbed, and have been thought to hold etiologic relation to a number of diseasc-processes.

The matter, however, does not end here. During the transposition processes which are going on in the human organism, there are produced not only useful and indifferent substances, but also injurious and poisonous products. Under normal conditions they create no evident disturbance, because they are formed only in very small quantities, or in marked attenuation; or they unite with other substances, or are rapidly expelled. Under abnormal conditions and in the presence of the failure in action of the inhibitory processes, the injurious and toxic action of the imperfectly oxidized products of metabolism is evident; in other words, autointoxication of the organism. Thus writes Albu, and it is from his introduction to this subject that the preceding statements have been quoted.

Let us see for a moment how the subject is approached by others. Von Jaksch[3] distinguishes (a) retention-toxicoses, with clinical (morbid) symptoms depending on the retention of physiologic bases; (b) noso-toxicoses, referable to the presence of basic products, which are formed in the organism (blood, etc.) in disease and eliminated with the urine; (c) autotoxicoses, with clinical symptoms which are caused by the formation of toxic basic substances from morbid materials, such as pathologic fluids present in the body, which bases are absorbed and give rise to manifestations of severe poisoning; and (d) exogenous toxicoses, with clinical symptoms or morbid entities due to toxic basic substances ingested with the food, such as the poison of sausages and cheese. Other authors, for example Albu, are unwilling to accept without modification von Jaksch's classification, or to agree with him and others; for instance, Kobert, Schwalbe and Bouchard, who count among the autointoxications all those diseases which arise from the action of a *contagium vivum,* that is, all the infections, or infectious diseases. Albu, also, and it would seem properly, wishes to strike from the list of autointoxications nutriment poisonings by flesh, sausage, cheese, mussels, etc., which

3. Jaksch, R. von: "Clinical Diagnosis." Fifth English edition. edited by A. E. Garrod, 1905.

Bouchard[4] includes. As Chapman[1] puts it: Specific infectious diseases must not be included with autointoxications; only substances which originate in, or are elaborated within, the system should be regarded as causing autointoxications. Thus, mussel or sausage poisoning is a different process from intestinal putrefaction in which poisonous diamins are formed within the bowel lumen. In other words, autointoxication must not be confounded with autoinfection.

Although some authors would designate as autogenetic diseases only such as originate within the living cell itself and have gone so far as to regard the contents of the intestinal tract as being outside of the organism and, therefore, not participants in the condition under discussion, this ultra view is not accepted by the best authorities. It is true that putrefaction and decomposition of the intestinal contents are referable to the action of bacteria which have been introduced into it; but the autointoxications which arise from the poisonous substances thus produced differ from the infectious diseases caused by bacteria because the latter represent specific intoxications of the organism, while the former come into existence as the result of conditions which constantly obtain in the organism (Albu).

The classification adopted by Albu is as follows: (1) Autointoxication caused by loss of function of an organ, e. g., myxedema, pancreatic diabetes, Addison's disease, acute yellow atrophy of the liver; (2) autointoxication due to general abnormalities of metabolism. e. g., gout, oxaluria, etc.; (3) autointoxication from retention of physiologic products of metabolism in various organs of the body, e. g., toxic phenomena after extensive burns, carbonic acid poisoning in difficult respiration, uremia, etc.; (4) autointoxication caused by overproduction of physiologic and pathologic products of the organism, e. g., acetonuria, coma of diabetes, etc. In a position between groups three and four, and probably belonging to both, are the great majority of the autointoxications which proceed from the intestinal tract.

AUTOINTOXICATION AND THE EYE.

Let us next briefly review this subject from the standpoint of those who are especially concerned with its

4. Bouchard: "Lectures on Autointoxication in Disease." Translated by Thomas Oliver, 1905, p. 159.

relationship to the eye. Uhthoff[5] divides the autointoxications into: 1. Intestinal or enterogenous, (a) caused by affections of the digestive tract which lead to abnormal fermentation and decomposition processes; (b) caused by abnormal changes resulting from the presence of intestinal parasites (helminthiasis, etc.). 2. Histogenetic, (a) caused by the products of individual metabolisms (diabetes, gout, uremia, carcinoma, chlorosis, pregnancy, puerperium, lactation, etc.); (b) caused by insufficient elimination of the poisons of the body as the result of disease of certain organs (thyroid, adrenals, liver, hypophysis (?)).

Elschnig,[6] the most recent systematic writer on the subject from the ocular standpoint, after reciting the classifications of von Jaksch and Uhthoff, already quoted, points out that thus far diseases of the eye of probable autogenetic origin have almost exclusively been brought into association with the affections which belong to the histogenetic autointoxications. The intestinal autointoxications have received little notice either in general ophthalmic literature or in ophthalmic text-books, and he, therefore, records the results of his study of such diseases of the eye which have come under his observation and which may have etiologic relationship to this variety of autointoxication. In order to make clear his viewpoint, he quotes Weintraud's[7] definition: "Gastrointestinal intoxications in the most restricted sense of the word are those conditions in which poisonous substances, foreign to the normal metabolism, are produced in the gastrointestinal canal by reason of abnormal fermentation, and are reabsorbed in such quantities that they call into existence pathologic phenomena. It is further to be understood that products of normal indigestion, if produced and reabsorbed in abnormal quantities, may also lead to autointoxication."

While it is admitted that certain diseases and certain symptoms are the result of autointoxication, in the present state of our knowledge it is not possible to indicate the exact nature of the toxic product which causes

5. Graefe-Saemisch: "Handbuch der gesamten Augenheilkunde," second edition, 32-34, 1901, p. 179.

6. Elschnig: Klin. Monats. f. Augen., vol. xliii, No. 2, 1905, p. 417.

7. Weintraud: "Gastrointestinale Autointoxicationen," Lubarsch u Osterag, Ergebnisse, vol. iv, 1897.

any autotoxemia, save one. In this connection it is interesting to quote from Alonzo Taylor:[8]

"We do not know the entity of a single autointoxication except the acidosis of diabetic coma. We do know that no known autointoxication is to be attributed to any known end product of any known metabolism. Bouchard's work on the toxicity of the urine is untrustworthy, and there is no measurable toxicity in the urine apart from that of the electrolytes. All our present knowledge rests on clinical analogy. When a nephritic suddenly becomes blind without a retinal lesion we say that he has a toxic blindness; until we have objective criteria of the assumed autointoxication we are limited to clinical analogies and these are naturally to be used with the greatest caution, since they are subject to no known objective control. Of course, antointoxications exist, probably in plenty, but of their true nature we know nothing."

For the sake of the discussion of the subject, we may divide ocular conditions to be considered from the standpoint of autointoxication into those which occur in connection with diseases which are believed to be the result of such a condition, and, in turn, to divide these into two sub-groups, that is to say, again quoting from Taylor: "Psychoses being excluded, any visual abnormalities that exist independent of structural lesions and conditions of probable autointoxication, such as uremia, diabetes, tetany, etc., might reasonably be termed symptoms of autointoxication." In the second group would appear such structural lesions in the eye that arise in connection with diseases of quite certain nature as autointoxication, namely, nephritis, diabetes and the essential anemias. With these we are familiar, although we do not know how the nephritis or diabetes or pernicious anemia causes the retinal alterations any more than we know how diabetes causes gangrene, how pernicious anemia creates spinal sclerosis or how nephritis originates endarteritis. With such phenomena of autointoxication the present communication is not concerned. We are, therefore, limited to the discussion of various ocular diseases, which, other etiologic factors being eliminated, seem, largely by reason of therapeutic tests and not from knowledge of any exact product, to be the result of an intestinal toxemia, or to be caused by an enterogenous decomposition product.

8. Personal communication, Dec. 31, 1905.

If we are to assume an autointoxication of gastrointestinal origin as a probable etiologic factor in any ocular disease, it is necessary to know some sign by which such enterogenous decomposition may be recognized. The most definite symptom, as Elschnig points out, is the presence of abnormal organic compounds in the urine, for example, phenol and conjugate sulphates, substances which are difficult to test. Easier of recognition is indican, the presence of which in increased and persisting amounts in the urine indicates decomposition of albumin in the digestive tract. To be sure, it is present in fevers, in anemia, in leukemia and even in neurasthenia, but it is said not to be present during simple constipation. It is this presence of indican which Elschnig regards as the best test of disturbances in the alimentary canal and the production of products the reabsorption of which gives rise to the toxemia to which he attributes the influences that bring about various ocular conditions, and in his experience the corneoscleral region and the uvea are most likely to suffer.

DISEASES OF THE OPTIC NERVE AND RETINA.

Referring to the possible relation of autointoxication to diseases of the optic nerve and retina, Uhthoff expresses the opinion that, while histogenetic autointoxication, with which the present paper is not concerned, may cause diseases of these tissues, intoxication of intestinal origin is almost entirely innocent of such etiologic relationship, although he is willing to admit that it may originate affections of the interior ocular muscles.

That retrobulbar neuritis may occasionally be the result of an intoxication which proceeds from the intestinal tract is indicated by Kraus' case, to which Elschnig[9] makes reference. A woman became suddenly blind, with all of the symptoms of retrobulbar neuritis. Eight days later she died, and autopsy failed to reveal any cause for death save gastrointestinal catarrh. The urine contained neither sugar nor albumin, but 25 per cent. of oxybutyric acid, and Kraus

9. Elschnig briefly recapitulates this case because, according to him, it appears to be unknown in ophthalmic literature. Edsall and I, however, have used this case in connection with our report of the examination of urine in cases of tobacco amblyopia, Trans. Amer. Ophth. Soc., 1903.

believes it probable that in this case an acid intoxication of intestinal origin was responsible for the symptoms and for the death of the patient.

Of much more importance is the possible relationship of intestinal toxemias to the development of so-called toxic amblyopia, that is to say, to the ordinary tobacco-alcohol amblyopia. I discussed this subject some years ago,[10] and pointed out that it was quite possible that nicotin or one or more of the many principles freely present in tobacco smoke liberate some toxic influence in the system which must be held accountable for the disease, which, in other words, depend on a species of autointoxication. Long ago Horner contended that neither alcohol nor tobacco as such was the direct toxic agent in cases of central amblyopia, but that together these drugs produced chronic gastric catarrh, which, in its turn, established a chronic anemia of the optic nerve, terminating in the pathologic changes which are found in this disease. Sachs maintained that even in the pure tobacco cases certain complex chemical combinations occur in the stomach, and that there was a resulting transformation of the normal gastric juices into acids of the fatty type, which combined with nicotin into substances which were more injurious than the simple tobacco bases themselves. Förster and Groenouw have also referred to disturbances of appetite and inanition as factors in the production of this amblyopia, and Elschnig himself is able to confirm Sachs' statement of the constant presence of gastrointestinal disturbances in association with alcohol-tobacco amblyopia. So far as I know, only Edsall and I have thus, up to this time, tried to prove this suspected relationship to the amblyopia by an analysis of urine,[11] the results of which were reported to the American Ophthalmological Society in 1903. Seven cases of tobacco-alcohol amblyopia were carefully examined, with the following findings:

Case 1—High increase for conjugate sulphates, temporary intense indicanuria and slight urobilinuria. Case 2—Intense urobilinuria. Case 3—Moderate urobilinuria and high volatile fatty acids. Case 4—Moderate urobilinuria, marked indican-

10. Norris and Oliver: "System of Diseases of the Eye," vol. iv, p. 183.

11. de Schweinitz and Edsall: "Concerning a Possible Etiologic Factor in Tobacco-Alcohol Amblyopia, Revealed by an Analysis of the Urine of Cases of this Character."

uria, decided reaction for phenol and high volatile fatty acids. Case 5—Intense indicanuria, moderate increase of conjugate sulphates, marked urobilinuria. Case 6—Intense urobilinuria and indicanuria and intense phenol reaction. Case 7—Marked reaction for phenol and notably high values for volatile fatty acids, with slight urobilinuria.

The results in general show that there was in all cases an excessive excretion of enterogenous decomposition products in the urine, and in all there was a more or less marked urobilinuria. In all the patients repeatedly examined these abnormalities nearly or quite disappeared under treatment, coincidentally with improvement in the eye conditions. A case of optic nerve atrophy examined as a control, the atrophy not being caused by tobacco and alcohol, showed almost entirely negative results, with only a slight reaction for indican and none for phenol. We stated that these facts gave just ground for the belief that toxic substances produced in the digestive tract, or in the course of metabolic processes, have at least a part in the production of amblyopia in these cases, and that at times they are probably the direct cause of the continuance of the symptoms when the latter do not appear after alcohol and tobacco have been stopped.

An amblyopia without ophthalmoscopic change in association with obstinate constipation has been attributed to an autointoxication proceeding from the intestinal tract by Young. Bulson[12] attributes the visual disturbances caused by excessive use of coffee (coffee amblyopia) to irritation of the digestive tract, created by this agent and consequent processes of decomposition and abnormal fermentation.

Elschnig refers to cases of scintillating scotoma and other neurasthenic symptoms which are seen in association with chronic intestinal catarrh and constipation, but very properly casts doubt on this etiologic factor, inasmuch as it is not proved that they may not be reflex manifestations from other sources, or from the intestines themselves, but not the indications of an absorbed poison.

OCULAR MUSCLE ANOMALIES.

When all other causes for the presence of an exterior ocular muscle palsy have been excluded, it has been

12. Bulson: Amer. Jour. of Ophth., vol. xxii, 1905, p. 55.

attributed at times to an autointoxication, but without any very definite examinations to justify the diagnosis. Paralyscs of the interior ocular muscles are probably more likely the result of gastrointestinal intoxications, and their symptoms would not in any sense differ from those which are caused by ptomain poisoning, which, as we have already noted, is not to be reckoned among the autointoxications.

I have seen several cases of unexplained paresis of accommodation apparently follow the ingestion of pure foodstuffs, that is to say, the ingestion of food which was not in any sense tainted, and doubtless all of us can recall similar examples in our practice. Some years ago, before the ophthalmic section of the College of Physicians of Philadelphia, Dr. Charles Herman Thomas exhibited a young man who always an hour after food suffered from paresis of accommodation. The subsequent history of the case I do not know. In none of these cases, however, has accurate urinary analysis been made, and they, therefore, are only classified in this group because other etiologic factors were not evident. Elschnig records a more carefully examined case of cycloplegia and loss of the pupil light reflex in a patient whose urine showed marked indican reaction, and who had no other cause for this condition, and who promptly recovered under treatment directed to the digestive organs.

Elschnig refers to one case of ocular muscle palsy reported by Varese without greater detail, in which the condition was attributed to an intestinal intoxication as the result of helminthiasis. Such intoxications are classified by Uhthoff under the autointoxications, the second group of them, at least, but more properly, according to Elschnig, they should be brought into relationship with the noso-toxicoses of von Jaksch's classification.

AFFECTIONS OF THE CORNEA AND SCLERA.

That a certain number of corneoscleral affections may possibly be referred to the action of toxins absorbed from the intestinal tract seems likely, the difficulty being, however, to eliminate other factors which are well established in their etiologic relation. A case in point is quoted by Elschnig of relapsing marginal ulceration of the cornea with increased indican reaction in the urine, and with cure which followed a careful diet and a regulation of habits tending to correct the abnormal intes-

tinal fermentation. It certainly must be the experience of all ophthalmologists that regulation of the diet, intestinal antisepsis, and in general terms, what I may call gastrointestinal hygiene, is of the greatest moment in the treatment of relapsing corneal ulcers, especially in children and young adults, but that these corneal lesions should be designated as symptoms of the autointoxication is not by any means certain, although if persistent urine analysis persistently gave the indications of enterogenous decomposition and other factors were eliminated, such relationship would at least be probable.

Exactly the same remarks apply to various forms of scleritis, both of the deep and superficial variety and to that form which is known as the periodic fugacious episcleritis, the "hot eye" of the English writers. In these diseases the regulations of diet, etc., which have been referred to are of the greatest moment in treatment.

These types of scleritis and keratitis have recently been the subject of a brief communication by Frederick Groyer,[13] and he is satisfied, using the method of Obermayer for indican reaction, that its persistent presence in the urine with these diseases, especially if the other signs of abnormal intestinal fermentation are present, must be accepted as a sign that the exciting cause arises in the gastrointestinal tract.

DISEASES OF THE UVEA.

The extreme difficulty of finding a satisfying cause for various types of uveitis, that is to say, uveitis with punctate keratitis, iridocyclitis, iridochoroiditis, recurring plastic choroiditis, and so-called relapsing or recurrent iritis, has led in recent times to a search for some toxin other than that supplied by syphilis and in vague terms by the rheumatic or lithemic diathesis.

According to Elschnig, what may be termed the gastrointestinal factor bears an important relation to these uveal tract diseases, and should be regarded in many of them, if not the sole, at least a contributing cause. Two varieties are in his experience particularly to be classified here.

1. Chronic iridocyclitis with deposits in the anterior chamber and opacities in the vitreous which occurs in women whose breath has an acetone-like odor and who

13. Groyer: Muench. med. Wochft., Sept. 26, 1905.

are the subjects of gastrointestinal indigestions and who tend to be obstinately constipated. It is not necessary to burden the communication with many case histories, but the type is a familiar one. An excellent example recently under my care occurred in a woman aged about 20, of sedentary habits owing to her occupation, who appeared with a moderate episcleral flush, which rapidly developed, as is so often the case, into a sharp uveitis, with mutton-fat drops deposited on the posterior surface of the cornea, succeeded rapidly by a web-like exudate in the anterior chamber and flake-like opacities in the vitreous. Ordinary remedies were entirely insufficient, but cure came with startling rapidity after thorough intestinal antisepsis preceded by the free administration of calomel and regulation of habits and diet. In this case scientific urine examination was not made, therefore the exact amounts of indican cannot be given. It is used simply as a type of those varieties to which Elschnig makes special reference and which all of us must frequently have seen.

2. Elschnig's second variety is relapsing or recurrent iritis. He believes the subjects are ordinarily healthy individuals. An attack of iridocyclitis occurs, is recovered from, and the process repeated until, if the inflammation is not checked, blindness is likely to result. In his experience the ordinary antisyphilitic remedies are useless, while treatment of the digestive organs arrested the process in five out of seven of his cases. He gives the case histories of seven patients, and for details the original article should be consulted.

Again, a very important series of phenomena, postoperative in character, should be considered from the same standpoint, namely, postoperative delirium and postoperative iridocyclitis. As is well known, postoperative insanity, particularly after cataract extraction, has been ascribed to the use of the bandage, the effect of atropin, to exaggeration of an imperfect mental balance existing prior to operation, and in a certain number of cases to autoinfection. The last etiologic factor has been especially the subject of discussion by Fromaget, who attributes the condition to an autotoxemia. Elschnig is satisfied that certain cases of iridocyclitis which follow operation may be caused by digestive disturbances, either reflexly or by the absorption of intestinal toxins.

He also believes that glaucoma following extraction

may have a similar determining cause. In a remarkable case of this character recently under my care, on the morning of the sixth day, after a perfectly normal extraction without complications of any sort, pain began, followed rapidly by rise in intraocular tension, and, in short, an attack of glaucoma. In the preceding twenty-four hours the urine, which had been normal in quantity and which contained no albumin, although an occasional cast, fell to eighteen ounces, also there were stubborn constipation and other indications of gastrointestinal disturbance. With the relief of these symptoms and the restoration of the urine to the normal amount, associated with myotics locally, the entire attack subsided, to be repeated twice afterwards, in, however, much milder degree, again with a return of all of the symptoms, in so far as the urine and intestinal tract are concerned, which have just been described. The ultimate result was a brilliant cure, with a vision with correcting lenses of fully normal degree. It will at least be admitted that a gastrointestinal intoxication may have been responsible for this complication, although it is not proved. John Green, Jr.,[14] reports a case of juvenile glaucoma, preceded by optic neuritis which he thinks, with reason, may have been due to the resorption of noxious material from the intestinal canal.

Elschnig believes that many cases of chronic choroidal disease may be due to gastrointestinal intoxication, but is unwilling to state more than that this condition should be regarded as a probable cause. The relationship of this form of toxemia to plastic choroiditis will be dealt with to a certain extent by Dr. John T. Carpenter, in his paper on plastic choroiditis to be read at our present meeting, and therefore I will leave details to him. In common with many of my colleagues, I have felt that in many of these cases we must look for etiologic factors not gathered from the usual sources of syphilis, tuberculosis, scrofulosis, and the like, but from some toxin, and therefore from one that may be well attributed to enterogenous decomposition products. The important point, again, is the neccssity of a search from this standpoint and the establishment of a dietetic and therapeutic regimen according to the conditions which have beeu found.

14. Green: Amer. Jour. of Ophth., vol. xxii, 1905, p. 318.

In so far as diseases of the lids are concerned, two important and troublesome affections should be mentioned, namely, recurring styes and various types of blepharitis. To styes Elschnig refers, and is satisfied that the discovery of indican in abnormal degree in these cases indicates their probable origin. The same is equally true of blepharitis. Modern dermatologists have recognized the important relationship of gastrointestinal toxemia to certain diseases of the skin, and many of their most brilliant results are not achieved through topical medication, but by vigorous antisepsis of the gastrointestinal canal.

In a recent conversation with Professor Duhring, one of America's most distinguished dermatologists, he impressed on me the absolute importance of investigation of the urine and treatment of the intestinal tract under these conditions, and urged me to make similar searches in the various chronic inflammatory conditions of the lid which we are so prone to encounter. We are only too often content with the corrections of refractive errors and the giving of some resolvent or stimulant salve, and while these are most important adjuncts in the treatment, they are not sufficient.

TREATMENT.

In so far as treatment is concerned, Elschnig believes that diet occupies an important position, and must be exclusively milk or mixed, according to circumstances. Calomel, in his experience, is a sovereign remedy, and he believes thoroughly in intestinal disinfection by the administration of guaiacol carbonate. Discussing this remedy with Dr. H. A. Hare, I find he also is satisfied that in many instances it furnishes him the best results in so far as intestinal antisepsis is concerned.

CONCLUDING REMARKS.

This communication is presented to the Section, not with the idea that it has in any sense reviewed the elaborate and conflicting literature of autointoxication, or that it has done anything more than to add to Elschnig's earnest advice that in the diseases already recited examinations should be made in accordance with the best methods of modern physiologic chemistry, that, in other words, we should not be satisfied with the ordinary routine, so-called alterative treatment, but that even so ap-

parently simple a disease as scleritis, or certain types of recurring corneal ulceration, and particularly the various types of uveitis which have been described, should be the signal for patients to be submitted to an examination as thorough as modern clinical medicine can yield.

To summarize: Although we do not know the entity of a single autointoxication except the acidosis of diabetic coma, and although we know that no known autointoxication is to be attributed to any known end product of any known metabolism, to quote Alonzo Taylor, we do know, from clinical analogy, at least, that autointoxications exist, even if their true nature is as yet a secret. We do know, too, that after food is swallowed and before the end products of assimilation are eliminated, there may be processes arising under abnormal conditions which yield poisonous products foreign to normal metabolism, the reabsorption of which may be followed by definite symptoms. We have reason to believe, in the absence of other causes, that under these conditions ocular troubles may also arise largely in the corneoscleral and uveal tracts, and probably, in so far as the nervous apparatus is concerned, in manifestations to which we apply the term acute or chronic retrobulbar neuritis. We do not know whether these toxins, whatever they may be, actually are the only and sole cause of these conditions, but such examinations as have been made by Elschnig, by Kraus, by Groyer, by Edsall and by myself, at least indicate that, to use Elschnig's term, they may be considered accessory causes. As Edsall and I have said, they may be able to play a certain part in the production of the symptoms, and at times are probably the direct cause of their continuance, even when other more commonly accepted etiologic factors have ceased to be active.